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FULL PAPER

CT-based follow-up following radiotherapy or radiochemotherapy for locally advanced head and neck cancer; outcome and development of a prognostic model for regional control

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Objective: The purpose of this study was to make a prognostic model for regional relapse in head and neck cancer using clinical and CT parameters.
Methods: 183 patients with lymph node-positive head and neck cancer were treated between 2002 and 2012 with radiotherapy or concurrent chemoradiotherapy. CT studies pre- and post-treatment were reviewed for lymph node size and the presence of necrosis, extracapsular spread (ECS) and calcifications. For every patient, correlations with 3-year regional control (RC), metastasis-free survival (MFS), disease-free survival (DFS) and overall survival (OS) were made.
Results: 3-year outcome rates were as follows: local control of 84%, RC of 80%, MFS of 74%, DFS of 61% and OS of 63%. Pre-treatment nodal size and the presence of necrosis were associated with a poorer outcome. This was also the case for post-treatment lymph node size, the presence of necrosis and ECS. We developed a CT-based prognostic model for RC with an area under the curve of 0.78 (95% confidence interval 0.63; 0.85).
Conclusion: We reached a good outcome in our patient cohort using a CT-based follow-up approach. A CT-based model was developed, which can aid in predicting RC.
Advances in knowledge: A prognostic model is proposed, which can aid in predicting RC and the necessity for post-radiotherapy neck dissection using clinical parameters and parameters derived from the post-treatment CT study. This is the first article to propose a prognostic model for regional relapse in head and neck cancer based on these parameters.

INTRODUCTION

Head and neck cancer encompasses a large number of tumour entities originating from subsites such as the nasal cavity, nasopharynx, oral cavity, oropharynx, larynx, hypopharynx and salivary glands. The majority of these tumours are squamous cell carcinoma.[1] Head and neck cancer is the fifth most common cancer worldwide. In the USA, about 55,070 new cases were estimated for the year 2014.[2]

Approximately 60–80% of patients present with locoregionally advanced disease at the time of diagnosis. Radio(chemo)therapy has become the standard of care for this subset of patients.[3,4] Overall survival (OS) after radio(chemo)therapy ranges between 50 and 60% after 5 years of follow-up. Local recurrence and/or regional recurrence (RR) is the most frequent form of therapy failure after radio(chemo)therapy, while failure due to metastasis is much less common.[5,6] Close follow-up of the neck after radio(chemo)therapy in this patient group is therefore very important. At our centre, the need for neck dissection after radiotherapy is determined based on the nodal response on the post-radiotherapy CT study 4 months after radiotherapy. Only patients who show suspicion of residual disease undergo a subsequent salvage neck dissection. Owing to the increased risk of potentially severe post-operative complications such as wound infection, fistulae, skin flap necrosis, pneumonia and pulmonary embolism, we aimed to limit the amount of unnecessary neck dissection.[7,8] Moreover, surgery exacerbates chronic effects of radiation such as subdermal fibrosis, neck stiffness and shoulder dysfunction.[9]

Management of the neck following radiotherapy or radio(chemo)therapy has evolved over the past decades

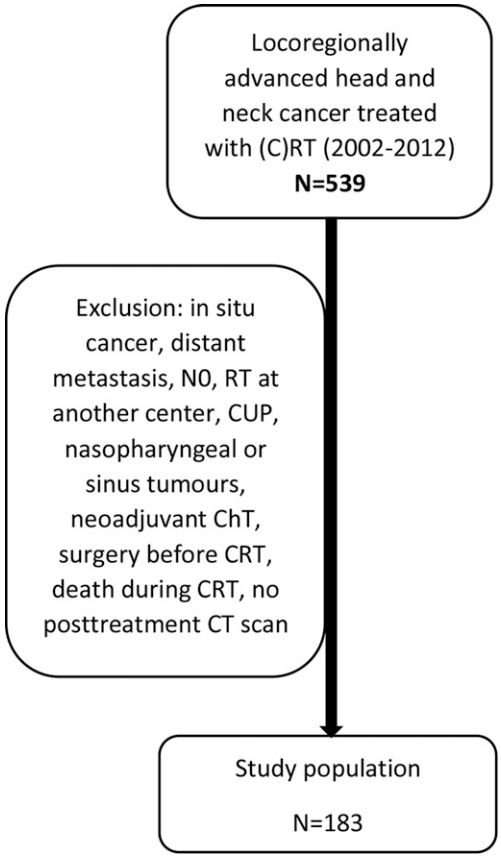
and has been a field of debate. Traditionally, patients with advanced neck disease underwent planned neck dissection after radiotherapy.[7] In the 1990s, however, several institutes demonstrated low rates of neck failure in patients who had complete clinical response by physical examination and were not submitted to neck dissection.[10,11] Nowadays, considerable variability exists in the follow-up of head and neck cancer. Both CT and positron emission tomography (PET) studies are being used for response evaluation.[12–14] Data on the use of CT are, however, scarce. The aim of this study was to report the outcome of a CT-based follow-up of the neck after radiotherapy or radiochemotherapy for head and neck cancer and to investigate whether a prognostic model can be made to determine the risk of RR for every individual patient.

METHODS AND MATERIALS

Inclusion criteria and end points

Between January 2002 and December 2012, 183 consecutive patients with nodal positive squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx were treated with radio (chemo)therapy or radiotherapy. Inclusion and exclusion criteria are specified in Figure 1. Patients were included by review of patient files. The patients were assessed clinically weekly during and after treatment until acute side effects regressed and every 2 months for the first 2 years, every 3 months for the third year, every 4 months for the fourth, every 6 months the fifth year and then yearly.

Figure 1. A flow diagram of patients included in the analysis. HNC, head and neck cancer; CRT, chemoradiation; RT, radiation therapy; CT, chemotherapy (ChT), study.



Follow-up with CT study was carried out 4 months after completion of radiotherapy in all patients. Only those with suspicion of residual neck disease underwent subsequent neck dissection. In equivocal cases, follow-up CT studies were carried out, omitting a neck dissection in non-evolving situations.

The primary end point of this study is 3-year RR. Secondary end points are 3-year local control (LC), metastasis-free survival (MFS), OS and disease-free survival (DFS).

Analysis of the CT imaging data

CT studies prior and after radio(chemo)therapy were reviewed for all included patients. All CT studies were performed using multidetector spiral CT. An iodinated contrast agent was injected in most patients; 100 ml at a rate of 1–1.5 ml s^{-1}. Scanning was started 80–100 s after the start of the contrast agent injection. The native CT images were acquired with a slice thickness of 0.6–0.75 mm and reformatted for display with a slice thickness of 3 mm.

All CT studies were analyzed by a single observer under the supervision of both a radiologist and a radiation oncologist specialized in head and neck cancer. Volumes and diameters of the lymph nodes were calculated using the Impax Volume Viewing 3D software from Agfa Healthcare.

We scored nodal volume, largest axial diameter, necrosis, extracapsular spread (ECS) and the presence of calcifications in all pathological lymph nodes in our patient population both on the pre- and post-treatment CT study.

The scoring of the CT images was carried out blinded to patient outcome and blinded to follow-up imaging.

Statistical analysis

Description of the time-to-event outcomes (LC, MFS, DFS and OS) of the patient cohort was based on Kaplan–Meier estimates. Predictors for time-to-event outcomes were analyzed by Cox regression models, and results were presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Predictors for binary outcomes (RR) were analyzed by logistic regression models, and results were presented as odds ratios (ORs) with 95% CIs. Analyses have been performed using SAS® software v. 9.4 (SAS Institute Inc., Cary, NC) of the SAS System for Windows.

We correlated age, gender, tumour (T) and nodal (N) stage, HPV status and localization of the tumour with different outcome parameters. For every patient, the total nodal volume of all lymph nodes, the largest axial diameter, the presence of necrosis and ECS were correlated with clinical outcome.

In order to further investigate the prognostic significance of the presence of necrosis before or after treatment, patients were assigned to four groups: (1) no necrosis on the pre- and post-CT study, (2) necrosis on the pre-treatment study only, (3) necrosis on post-treatment only and (4) necrosis on both the pre- and post-treatment study. Pairwise comparisons between these groups were made.

A stepwise selection procedure was followed to construct a multivariable prediction model for regional relapse within 3 years. The area under the receiver-operating characteristic curve (AUC) was determined for the selected model. In addition a bootstrap-corrected AUC value was calculated. This AUC value corrects for overoptimism resulting from the fact that model construction and model validation were performed on the same data set.

HPV analysis

For all patients with oropharyngeal tumours, formalin-fixed, paraffin-embedded tissue was obtained for HPV status

Table 1. Patient and treatment characteristics

Characteristics	Number of patients (%) ($n = 183$)	
Mean age (years)	59	
Sex		
Male	155	85
Primary tumour site		
Oral cavity	30	16
Oropharynx	122	67
HPV+	20	
HPV−	92	
Unknown HPV status	10	
Hypopharynx	25	14
Larynx	6	3
T classification[a]		
T1	8	4
T2	47	26
T3	51	28
T4	76	42
N classification		
1	32	17
2	142	78
2a	7	4
2b	63	34
2c	72	39
3	9	5
Radiation therapy		
3D CRT	84	46
IMRT	99	54
Systemic therapy		
None	35	19
Cisplatin	118	64
Carboplatin/5-FU	2	1
Cetuximab	11	6
Panitumumab	8	4
Cisplatin + tirapazamine	8	4
Cisplatin + zalutumumab	1	1

3D CRT, three-dimensional conformal radiation therapy; 5-FU, 5-fluorouracil; IMRT, intensity-modulated radiation therapy.
[a]One patient had four synchronous head and neck malignancies and was not included in the T classification statistics.

determination. HPV testing was performed using p16 immunohistochemistry followed by HPV polymerase chain reaction. A tumour was regarded as HPV related when both p16 immunohistochemistry as well as HPV polymerase chain reaction were positive. Sections were scored as p16 positive when clear p16 immunoreactivity was seen in at least 50% of cells.

RESULTS

Patient/treatment characteristics and outcome

We included 183 patients with head and neck cancer (Figure 1). Patient and treatment characteristics are presented in Table 1.

Median follow-up was 5.04 years.

We report the following 3-year outcome rates: LC of 84% (95% CI 77–88%), regional control (RC) of 80% (95% CI 73–86%) MFS of 74% (95% CI 66–80%), DFS of 61% (95% CI 53–67%) and OS of 63% (95% CI 56–70%).

A higher T stage was statistically significantly associated with a poorer LC (HR 1.570, $p = 0.0316$), RC at 2 years (OR 1.725, $p = 0.0346$), DFS (HR 1.543, $p = 0.0016$) and OS (HR 1.364, $p = 0.0111$). This was borderline significant for MFS (HR 1.402, $p = 0.0523$). Higher N stage was associated with a higher risk of local relapse (HR 1.438, $p = 0.0355$). Age, gender, HPV status and localization of primary tumour site could not be withheld as useful predictors for outcome.

Table 2. Predictive value of CT characteristics for regional recurrence (RR)

Characteristics	RR Pre-CRT	RR Post-CRT
Sensitivity (%)		
Necrosis	81	65
ECS	16	23
Absence of calcifications		90
Specificity (%)		
Necrosis	36	77
ECS	81	92
Absence of calcifications		14
PPV (%)		
Necrosis	33	53
ECS	24	54
Absence of calcifications		30
NPV (%)		
Necrosis	83	84
ECS	72	75
Absence of calcifications		79

CRT, chemoradiation; ECS, extracapsular spread; NPV, negative-predictive value; PPV, positive-predictive value.

Results of the analysis of CT data

Pre-treatment CT study

On the pre-treatment CT study, 37 (20.2%) patients had ECS, 123 (67.2%) patients had necrosis and 3 (1.6%) patients had calcifications.

A trend was observed towards more RR when lymph node necrosis was present pre-treatment (OR 2.4, $p = 0.08$). The pre-treatment presence of necrosis was furthermore significantly associated with a higher risk of distant metastasis (HR 2.29, $p = 0.03$). On the other hand, a higher total sum of nodal volume was associated with a poorer DFS (HR 1.01, $p = 0.01$). There was no impact of maximal nodal axial diameter, nor the presence of calcifications or ECS on outcome. Sensitivity, specificity, PPV and NPV of the presence of necrosis and ECS for RR are presented in Table 2. This was not conducted for the presence of calcifications because there was only one case in the analyzed subset of patients with calcifications present pre-treatment.

Post-treatment CT study

On the post-treatment CT study, 18 (10.7%) patients had ECS, 53 (31.6%) patients had necrosis and 21 (31.6%) patients had calcifications (31.6%).

Post-treatment, all predefined characteristics (ECS, necrosis, larger diameter and larger volume) except the presence of calcifications were significantly associated with poor outcome (Table 3). Calcifications post-treatment are thus correlated with better outcome. Sensitivity, specificity, PPV and NPV for the influence of necrosis, ECS and calcifications on RR are presented in Table 2.

The sum of nodal volumes showed a non-linear trend in relation to the risk of distant metastasis (Figure 2a). Concerning OS, a non-linear trend was observed for the maximal nodal diameter (Figure 2b). Among all possible cut-off values for dichotomizing the maximal nodal diameter, the value of 31.88 mm provided the best model fit.

Presence of necrosis pre- vs post-treatment

The risk of RR significantly increased in patients with post-treatment necrosis only compared with patients without necrosis (OR 13.50, $p = 0.01$), and for patients with pre- and post-treatment necrosis compared with those with pre-treatment necrosis only (OR 7.52, $p = 0.01$).

Development of a model to predict regional recurrence

Based on our results, we developed a multivariable model for RR prediction. After performing a stepwise selection procedure, pre-treatment T stage ($p = 0.02$), post-treatment necrosis ($p = 0.03$) and largest diameter ($p = 0.01$) were included in the model. The AUC of this model was 0.78 (95% CI 0.633; 0.845); the bootstrap-corrected AUC was 0.74 (95% CI 0.667; 0.889). The risk for RR within 3 years can be calculated using following formula:

$$\mathrm{RR}\,(\%) = \frac{e^{\mu}}{1 + e^{\mu}}$$

Table 3. Predictive value of post-treatment CT characteristics for outcome

CT characteristic	Outcome	OR/HR (95% CI)	*p*-value
∑ nodal volume	RR	OR 1.262 (1.072; 1.486)	0.0051
	MFS	Non-linear trend	
	DFS	HR 1.051 (1.028; 1.074)	<0.0001
	OS	HR 1.056 (1.035; 1.078)	<0.0001
∑ nodal volume 2 cm^3 *vs* 1 cm^3	MFS	HR 1.152 (1.054; 1.259)	0.0018
Largest diameter	RR	OR 1.108 (1.047; 1.172)	0.0004
	MFS	HR 1.043 (1.014; 1.072)	0.0036
	DFS	HR 1.059 (1.035; 1.083)	<0.0001
	OS	Non-linear trend	<0.0001
Largest diameter >31.8 mm	OS	HR 5.764 (2.851; 11.651)	<0.0001
Necrosis	RR	OR 5.960 (2.410; 14.738)	0.0001
	MFS	HR 2.203 (1.186; 4.092)	0.0124
	DFS	HR 2.668 (1.671; 4.262)	<0.0001
	OS	HR 2.406 (1.529; 3.785)	0.0001
Calcifications	RR	OR 0.643 (0.167; 2.483)	0.5189
	MFS	HR 0.950 (0.373; 2.421)	0.9143
	DFS	HR 0.843 (0.404; 1.759)	0.6494
	OS	HR 0.863 (0.430; 1.729)	0.6772
ECS	RR	OR 3.451 (1.056; 11.283)	0.0404
	MFS	HR 2.482 (1.144; 5.385)	0.0214
	DFS	HR 2.343 (1.275; 4.303)	0.0061
	OS	HR 1.800 (0.971; 3.337)	0.0620

∑, sum; CI, confidence interval; DFS, disease-free survival; ECS, extracapsular spread; HR, hazard ratio; MFS, metastasis-free survival; OR, odds ratio; OS, overall survival; RR, regional recurrence.

$$\mu = 0.085 \times \text{largest axial diameter (mm)} + 0.6749 \times (\text{T stage}) - 4.8482 + (\text{only when necrosis})\ 1.1384\,.$$

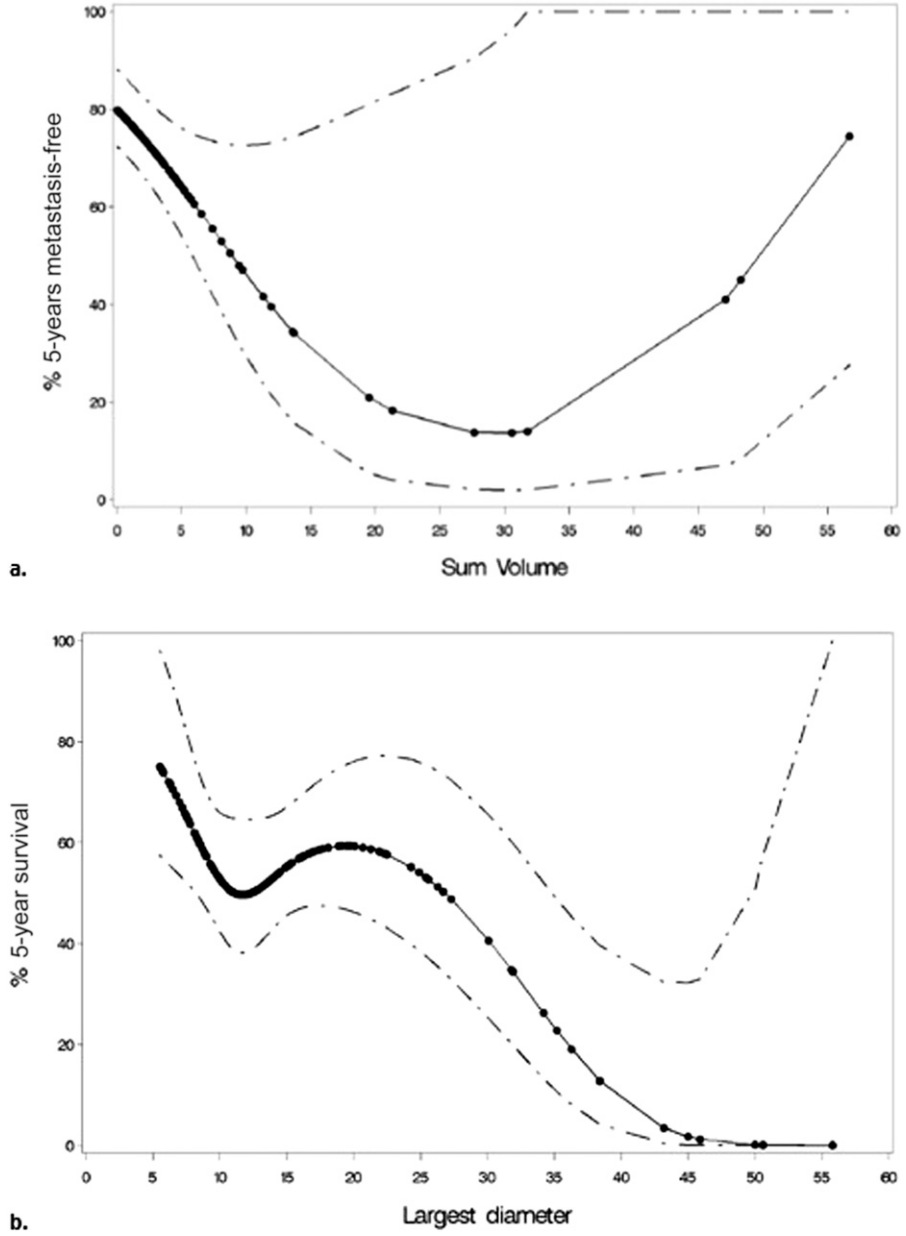
DISCUSSION

The role of planned neck dissection after radio(chemo)therapy for locoregionally advanced head and neck cancer has weakened over the past decade but is still a matter of debate. Data from mostly retrospective series support a conservative approach with neck dissection (ND) carried out only in those patients with residual disease on a clinical or radiological basis.[12,15–20] Some centres still perform planned neck dissection in all patients with N2 or N3 disease, irrespective of their response to initial treatment.[21] Robust data from randomized trials addressing this issue are lacking. In our centre, we advocate a conservative approach, thereby avoiding neck dissection and its complications in a large amount of patients. Outcome in our patient cohort is comparable with that described by other authors. Liauw et al[18] described a 5-year RC and OS of 84% and 45%, respectively, in a group of 209 patients treated by radio(chemo) therapy without neck dissection. Clavel et al[17] reported a 3-year RC and OS of 91% and 83%, respectively, in 369 patients treated with radio(chemo)therapy and subsequent neck dissection in 96 patients.

The value of the pre-radiotherapy CT parameters is disputable. In our data set, we could only confirm a negative relation between the presence of necrosis and MFS, and between total nodal volume and DFS. Moreover, we correlated clinical parameters with outcome. A higher T stage was statistically significant associated with a poorer outcome.

In the post-treatment setting, scoring nodal CT characteristics does have prognostic significance. We confirmed the value of necrosis and ECS, as well as measuring lymph node diameter and total nodal volume on CT studies after radio(chemo)therapy. Within the range of the majority of the observations, a higher lymph node volume leads to a higher risk for all outcome parameters. Owing to a striking non-linear trend of largest nodal axial diameter for OS, the variable was dichotomized, leading to a cut-off at 31.88 mm, above which OS is compromised more importantly. A linear trend was observed for the relation between nodal diameter and the other outcome parameters. Regarding MFS, a non-linear trend was observed for the sum of nodal

Figure 2. (a) The non-linear trend of sum of nodal volume in relation to risk of distant metastasis: the dots are representing predictions for individual patients. (b) The non-linear trend of the largest nodal diameter in relation to overall survival: a best cut-off for the largest axial diameter of 31.8 mm was selected. The dots are representing predictions for individual patients.



volumes in relation to the occurrence of distant metastasis. Although, this non-linear trend was induced by a small number of outlying values. In the lower range, where the majority of observations lie, a linear relationship was seen.

We investigated the presence of pre- and post-treatment necrosis further to see at which moment this parameter was most predictive for RR. Patients with newly formed necrosis have a higher risk of RR than patients without or with pre-existing necrosis. The presence of the necrosis might suggest more hypoxic nodal disease and might prevent delivery of chemotherapy and reduce the effectiveness of radiotherapy.

Using the results of our study, a model was constructed to estimate the risk for RR in a given patient. This model reached a good AUC of 0.78. Because creation and validation of the model was carried out in the same data set, we also calculated a corrected AUC; this was 0.74. This corrected value gives an honest estimate of the predictive accuracy of the model when applied to an independent patient. For example, using our model, a patient with a T4 tumour without necrotic pathological lymph nodes and largest nodal axial diameter 12.1 mm would have a risk of 24.61% for developing an RR within 3 years. To our knowledge, no other model using clinical parameters and parameters obtained from a CT study or other imaging modalities was proposed in other articles so far.

An extensive discussion of the role of other imaging modalities of the neck after radio(chemo)therapy such as ultrasound, PET-CT and MRI is beyond the scope of this article, but each of those are believed to be useful in assessing response and the need for salvage neck dissection. Ultrasound, in combination with fine-needle aspiration cytology, is an inexpensive and readily available tool. Yom et al[22] described an NPV of 95% for ultrasound fine-needle aspiration cytology.[23] Data on the role of post-treatment PET-CT are emerging rapidly, and results are promising. Loo et al described an NPV of 100% for PET-CT obtained 3 months after completion of radiotherapy.[15] This was further investigated in a multicentre study (PET-NECK), which recruited 564 patients with N2 or N3 head and neck cancer treated with radio(chemo)therapy and randomized between routine neck dissection and a wait-and-see approach if PET-CT 9–13 weeks after treatment shows no abnormal FDG-uptake in the neck.[13] This study reports similar results in patients who underwent PET-CT-guided surveillance and those who underwent planned neck dissection, but surveillance resulted in fewer operations and was more cost effective. In the last few years, advances in MRI, with development of diffusion-weighted MR (DW-MRI) and dynamic contrast-enhanced MRI, have provided additional information. Recently, Vandecaveye et al[24] evaluated response after radiotherapy in 29 patients with DW-MRI at 3 weeks after completion of treatment. He reported an NPV of 96% for adenopathies per neck side, and a sensitivity of 78% of DW-MRI *vs* 67% for conventional MRI for detecting subcentimetre lymph node metastasis. We can conclude that CT is at least of equivalent value in the assessment of the neck after radio(chemo)therapy. Moreover, CT is more accessible than PET-CT and DW-MRI and has been widely used for many years in this setting.

This was a monocentric retrospective study, with its inherent limitations. However, we made sure to have sufficient follow-up of every patient in order to have firm reliable data. The strength of this study lies in the large number of analyzed data and the fact that all measurements were performed by the same observer, with cooperation of both a radiation oncologist and a radiologist specialized in head and neck cancer. This study can therefore be a first step in designing a prospective trial addressing the management of the neck post-radio(chemo)therapy and validating the proposed model for RR prediction.

CONCLUSION

Our data confirm that in a group of patients with locoregionally advanced head and neck cancer, good disease control in the neck can be obtained with radio(chemo)therapy without subsequent planned neck dissection. Furthermore, we propose a multivariable model to calculate the risk of a regional relapse with an AUC of 0.78 based on T stage before therapy and post-treatment presence of necrosis and largest nodal diameter.

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